Amendments to the Specification:

Please replace paragraph [05] beginning at page 2, line 10, with the following:

--[05] Individual proteins can possess one or more discrete monomer domains. These proteins are often called mosaic proteins. For example, members of the LDL-receptor family contain four major structural domains: the cysteine rich A-domain repeats, epidermal growth factor precursor-like repeats, a transmembrane domain and a cytoplasmic domain. The LDL-receptor family includes members that: 1) are cell-surface receptors; 2) recognize extracellular ligands; and 3) internalize them for degradation by lysosomes. See Hussain et al., *The Mammalian Low-Density Lipoprotein Receptor Family*, (1999) Annu. Rev. Nutr. 19:141-72. For example, some members include very-low-density lipoprotein receptors (VLDL-R), apolipoprotein E receptor 2, LDLR-related protein (LRP) and megalin. Family members have the following characteristics: 1) cell-surface expression; 2) extracellular ligand binding consisting of A-domain repeats; 3) requirement of calcium for ligand binding; 4) recognition of receptor-associated protein and apolipoprotein (apo) E; 5) epidermal growth factor (EGF) precursor homology domain containing YWTD repeats (SEQ ID NO. 198) (SEQ ID NO.218); 6) single membrane-spanning region; and 7) receptor-mediated endocytosis of various ligands. See Hussain, supra. Yet, the members bind several structurally dissimilar ligands.--

Please replace paragraph [24] beginning at page 5, line 30, with the following:

--[24] In some embodiments, the monomer domain is an LDL receptor class A domain monomer comprising the following sequence:

 $C_{3}X_{3-15}C_{b}X_{3-15}C_{c}X_{6-7}C_{d}(D,N)X_{4}C_{e}X_{4-6}DEX_{2-8}C_{f}$ (SEQ ID NO:219)

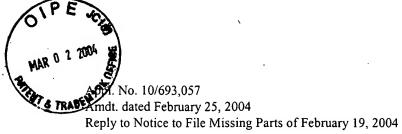
wherein C is cysteine, X_{n-m} represents between n and m number of independently selected amino acids, and (D,N) indicates that the position can be either D or N; and wherein C_a - C_c , C_b - C_e and C_d - C_f form disulfide bonds.--

Please replace paragraph [25] beginning at page 6, line 4, with the following:

wherein X is defined as follows:

--[25] In some embodiments, the monomer domain is an LDL receptor class A domain monomer comprising the following sequence:

$$\begin{split} & \frac{CaX_{6-7}C_bX_{4-5}C_eX_6C_dX_5C_eX_{8-10}C_f}{C_aX_{6-7}C_bX_{4-5}C_cX_6C_dX_5C_eX_{8-10}C_f \text{ (SEQ ID NOS:220-231)}}{C_aX_{6-7}C_bX_{4-5}C_cX_6C_dX_5C_eX_{8-10}C_f \text{ (SEQ ID NOS:220-231)}} \end{split}$$



ċ		Α	X3 A		X5			С				X4 A			X1	X2 A	X3			X6 A	С	Х1	X2	X(5) X3 A	X4	X5		K1 A		X3 A	X4 A		8,10 X6					С
*	DEFGH KLMXPORSTV	CDE GHIKLMNPQRSTVWY	DEFGH K NPQRSTVWY	DEFGH KLMN QRST Y		EF HIKLMNPQRSTV			H KL NPQRSTV Y	GH N QRSTV Y	H K L N Q R S T	CDEFGHIKLMN QRSTV		100000	F IKL TV Y	DEFGH KLMNPQRSTVWY	DEFGHIKLMIPGRSTV Y	DEFGHIKLMNPQRSTVWY	DEFG KLMN QRSTVWY	EF HIKLM PQR TVWY		D	DEFGH KLMN QRSTVWY	DEFGHIKLMN QRSTVWY	DEF HIKL NPORSTVWY	DE H N Q ST		= 3 +	GHNQSTY	H KLMN QRS WY	E G LM RST	D	E	DEFGHIKLMN QRSTVWY	DEFGHIKLMZPORS			
	X1 A	X2 A	Х3	X4	X5	X6	X7		X1 A	: X2	~Х3 А	X4 A	X5 A			HE.			- 14				T.	112		g. Pe		4		X3 A	X4		X6	X7 A	A	A A	\$: 2 ⁽⁴)	
ir o	D E F	D E	D F	D E F	E	F	E	E.S	E	Đ	E	D E F	E													ì		=	D			D	E		Ε	D E		•
	H	G H	G	Н	G	н	G		Н	G	H	G H I	G H															3		G H				G H	G	н		
	K L N P R S T	L N P R S T	KL NPQRSTV	K M N R S T V	K L N P Q R	L *	K L M R S T V		KL RPORSTVW	K L NPQRSTV	K NPQRST	KL NPORSTVS:	K L M N Q R T V	· · · · · · · · · · · · · · · · · · ·	margament and market a						•							M S T V	Ni V	Q R	STY			L M N P R S	N P Q > y	L N Q S	•	· · · · · · · · · · · · · · · · · · ·
			Y	• -			i.	Ó	(2	24	¥ [:	Y		100		•											. 1		Y X2	ХЗ		Х5	Χę	X7 A	X8 A	X9 A	X10	l all l
														,													' 		D	D F	E	D	E	D E	D E	D E	Ε	Ço.
																												3		G H				G	H	G H I	H	
					•							_															4 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	-		K	L			K L M	K L M	K L	L M	
			-																									2	N	N Q				N P	Z P Q	Q	N P Q	*
																									-			₹ S	s	R S	S T	,		S T	R S	S T V	R T V	100
																													23.0	W Y			147	W		Y	Y	

In some embodiments, the LDL receptor class A domain monomers each comprise SEQ ID NO:201 SEQ ID NO:331.--

PATENT

Please replace paragraph [26] beginning at page 7, line 3, with the following:

--[26] In some embodiments, the monomer domain is an EGF domain monomer comprising the following sequence:

$$C_aX_{3-14}C_bX_{3-7}C_cX_{4-16}C_dX_{1-2}C_eX_{8-23}C_f$$
 (SEQ ID NO:232)

wherein C is cysteine, X_{n-m} represents between n and m number of independently selected amino acids; and wherein C_a - C_c , C_b - C_e and C_d - C_f form disulfide bonds.--

Please replace paragraph [27] beginning at page 7, line 3, with the following:

--[27] In some embodiments, the monomer domain is an EGF domain monomer comprising the following sequence:

$$C_aX_{4-6}C_bX_{3-5}C_cX_{8-9}C_dX_1C_eX_{8-12}C_f$$
 (SEQ ID NOS:233-322)

Appl. No. 10/693,057 Amdt. dated February 25, 2004 Reply to Notice to File Missing Parts of February 19, 2004

c ,	άx		(4,6) 3 X4			С	ΧĬ	X2	X(3,:	5)		C :	(1)	(2)	(3 X	X(8	3,9) 5 Xe	X7	Х8		C	((1) (1	. e)	(1)	(2 · X	3 X4	X5		((8/1 X7						C.
<u> </u>	: 3 G 1 H	D E G H	E G				A D E G H K	F G H L		,		 		A A CO	A A C C C C C C C C C C C C C C C C C C	A D E F G H I	A D E G H	A F	A D E F		'' 	(5 ,G	F H I	A DEFGHIKL	D G	F	A DEF HIKI		•			
; () () ()	Г Т / /	M N P Q R S	N P Q R S T				N P Q STV	N Q	N Q R S T V				M F G G G G G G G G G G G G G G G G G G	P F Q Q R F S S T T V V	N P F CO	N P Q R S T V W	Q R S T V W Y	P R T V	MN QRSTVVY			M	1	M		M R T W Y	MN QRSTV		R S T V	Υ		•			
	(1 X A A						X1 A		X3 A				A A	(2)	(3) A	4 X	5 X6		X8	X9				(48)	(2 X	3 X4	X5 A	A A	A A	X8 A	X9 A	X10	X11 A	X12 A	jå d
() () () () () () () () () ()	D D D D D D D D D D D D D D D D D D D	EFGH L NPQRST	GH I K L N P R S T			4	-R ∙S	S		DEF HIKLMN QRSTV			D (E E E E E E E E E E E E E E E E E E			E F G K L N P Q R S	M N	G KLM QRS	I P	s				O [: 0 1 2 3 3 5 5 5 5 7	E F L L M Q R	N	FG IKLM PQRSTVW	DEFGH KLMNPQRSTVW	DE G IKLMNPQRSTV	DEFGHIKLMN Q STV	EFGHIKLMNPQRST W	DEFGH KLMNPQRSTV	DEFGHIK MN QRSTV	
) /	(1 X: \ A		X4 A		X6 A		À			X4 A			(4)			4 X	Y 5 X6	X7	Y X8				١	′	, .	Y	Υ	Υ		Υ			Ÿ.	Υ .	****
1 F (E	HIKLMAPORS	DEFGHIKLMZPQRSTV	DEFGHIKL NPORS > >	DE G IKLMNPQRSTV V		ODEFOI KTWZFOR% > >	DE GHIKLMRPQRSTV >	Ε	H Q	E F H	1 日 「						•																	

Appl. No. 10/693,057 Amdt. dated February 25, 2004 Reply to Notice to File Missing Parts of February 19, 2004

	X2	X3				С		X2		5)				. X3	X4		X6				Ç	X(1			X3	X4			(8/1 X7		-				C _~
DEFGHIKL NPQRSTVW X1	E GH KLMNP RST YX2	DE GH KLMRPQRSTVV	E G MNPQRST YX4	X5			H 'K NPQ STV	L N Q S T	H!K! N QRSTV	<u>X4</u> A		DEFGHIKLMN QRSTVXYX	DE KL NPQRSTV	ACDEFGHIKLMNPQRSTV YXX	DEFGHIKLMNPQRSTVWY	DEFGHIKL NPQRSTVW	DE GH KLMN QRSTVWY	F H I L P R T V Y	D E F			LMNPQRS	Q R S T V	DEFGH KL NPQRSTV	E GH KL NP RST.	F H I L M R T W Y X4 A	A DEFGHIKLMN QRSTV YX5	D G S.	A DEF HIKL NPORSTV YX	I K L M N Q R S T Y	X9 A	X10	. <u>X11</u>	<u>X1</u>	2
DE G KL QRSTV	DEFGHIKLMNPQRSTV X2	EFGH L NPQRST WYX	DEFGHIKL NP RST	FG!KLMNPQRSTVYX5	; X €		DEFGHIKLMNPQRSTV X1A	DEFGH KL NPQRST Y	G T	DEF HIKLMN QRSTV	X5	D F H K L M X Q R S T > Y	DEF H LMNPQRS V	DEFGH L X RS	D E	DEFG KL NPQRS	D E G M N	G KLM QR	P	E H K L Q S T V			DEFGHIKL NPORST	DEF HIKLMNPQRSTV	DE G NP S	DEF H LM QRST WY	DEFGHIKLMN QRSTV Y	FG IKLM PQRSTVWY	DEFGH KLMNPQRSTVV	DE G IKLMNPQRSTV Y	DEFGHIKLMN Q STV	WFGHIKLMXPQRST &	DEFGH KLMNPQRSTV Y	DEFGHIK MN QRSTV	
	E F G H I K L M N P Q R S T V	DEFGHIKLMNPQRSTVV	DEFGHIKLMZPQRSTV	DEFGHIKL NPORS V Y	DE G IKLMNPQRSTV Y	1、1の一本の物質に対していましまします。		DE GHIKLMRPQRSTV Y	EFGH KL N QRST	F G H Q S T V	F HIKLMZ QR																								

Please replace paragraph [39] beginning at page 10, line 28, with the following:

--[39] In some embodiments, the domains form a secondary structure by the formation of disulfide bonds. In some embodiments, the multimers comprise an A domain connected to a monomer domain by a polypeptide linker. In some embodiments, the linker is from 1-20 amino acids inclusive. In some embodiments, the linker is made up of 5-7 amino acids. In some embodiments, the linker is 6 amino acids in length. In some embodiments, the linker comprises the following sequence, A₁A₂A₃A₄A₅A₆ (SEQ ID NO. 244) (SEQ ID NO:352), wherein A₁ is selected from the amino acids A, P, T, Q, E and K; A₂ and A₃ are any amino acid except C, F, Y, W, or M; A₄ is selected from the amino acids S, G and R; A₅ is selected from the amino acids H, P, and R; A₆ is the amino acid, T. In some embodiments, the linker comprises a naturally-occurring sequence between the C-terminal cysteine of a first A domain and the N-terminal cysteine of a second A domain.--

Please replace paragraph [53] beginning at page 13, line 7, with the following:

--[53] In some embodiments, the monomer domain is an LDL receptor class A domain monomer comprising the following sequence:

$$C_aX_{3-15}C_bX_{3-15}C_cX_{6-7}C_d(D,N)X_4C_eX_{4-6}DEX_{2-8}C_f(\underline{SEQ\ ID\ NO:219})$$

wherein C is cysteine, X_{n-m} represents between n and m number of independently selected amino acids, and (D,N) indicates that the position can be either D or N; and wherein C_a - C_c , C_b - C_e and C_d - C_f form disulfide bonds.--

PATENT

Appl. No. 10/693,057 Amdt. dated February 25, 2004 Reply to Notice to File Missing Parts of February 19, 2004

Please replace paragraph [54] beginning at page 13, line 13, with the following:

--[54] In some embodiments, the monomer domain is an LDL receptor class A domain monomer comprising the following sequence:

 $CaX_{6\text{--}7}C_bX_{4\text{--}5}C_eX_6C_dX_5C_eX_{8\text{--}10}C_f$

 $\underline{C_aX_{6-7}C_bX_{4-5}C_cX_6C_dX_5C_eX_{8-10}C_f}$ (SEQ ID NOS:220-231)

Appl. No. 10/693,057 Amdt. dated February 25, 2004 Reply to Notice to File Missing Parts of February 19, 2004

C	X(4,5) C X(6) C X(5) X1 X2 X3 X4 X4 X1 X2 X3 X4 X5 X6 X1 X2 X3 X4 A A A A A A A A A A A A A A A A A A	X4 X5 X1 X2 X3 X4 X5 X6 X7 X8
E E E E E F G G G G G G H H H H H M M M M M M M M M	E E E E E E F G G G G G G H H H H H H I I I I I I I I	E E E E F G G G G G H H H H N N N N N N N P P P P P P P P P P P P

In some embodiments, the LDL receptor class A domain monomers each comprise SEQ ID NO:331.--

PATENT

Appl. No. 10/693,057 Amdt. dated February 25, 2004 Reply to Notice to File Missing Parts of February 19, 2004

Please replace paragraph [55] beginning at page 14, line 4, with the following:

--[55] In some embodiments, the monomer domain is an EGF domain monomer comprising the following sequence:

$$C_aX_{3-14}C_bX_{3-7}C_cX_{4-16}C_dX_{1-2}C_eX_{8-23}C_f$$
 (SEQ ID NO:232)

wherein C is cysteine, X_{n-m} represents between n and m number of independently selected amino acids; and wherein C_a - C_c , C_b - C_e and C_d - C_f form disulfide bonds.--

Please replace paragraph [56] beginning at page 15, line 1, with the following:

--[56] In some embodiments, the monomer domain is an EGF domain monomer comprising the following sequence:

$$C_aX_{4-6}C_bX_{3-5}C_cX_{8-9}C_dX_1C_eX_{8-12}C_f$$
 (SEQ ID NOS:233-322)

Appl. No. 10/693,057 Amdt. dated February 25, 2004 Reply to Notice to File Missing Parts of February 19, 2004

A A D E F F G H I K L M M N P P O	D D E F G G H I K L M N P Q Q R S T T V X X1 X2	C X1 A DE GH KLMNP RST YX1 A
A D E F	E F G H L N P Q R S T W Y	A DE GH KLMNP QRSTVW 12 X3
D II E II G II	G H I K I I N I P R S T	4,6) X4 A E G MNPQRST YX4
A A D D E E G G	K L M N P Q R S T V	
200 January 1 Ja		
A A C C C C C C C C C C C C C C C C C C	EFFGHIKLMNPQRSTV	A DE GG G G G G G G G G G G G G G G G G G
A A D D E E F G G H H	DEFFGGHKLNPQRSTTYX2X	Q Q R
A F G	HIKLMR QRSTV	3 X4
A DEF	ÝŠ	
	F HIKLMAN CRSTV	A DEFOREKLAN ORSTVSY
en e	EF H LMNPQRS	K L N P Q R S T V
en e	N R S T V	ACDEFGHIKLMNPQRSTV Y
	N P Q R S T	X4 A DEFGHIKLMNPORSTVWY
	DEFG KL NPQRST	A DEFGHIKL NPQRSTVW
	DE G MN RSTV Y	XA DE GH KLMN QRSTVWY
	Q R S T	A F H I L P R T V Y
	F Hi I P R VWYXA	X8 A DEF HIKLMN QRSTVWYX8
•	E H K L Q STV	
,		C XIT A DEF G H L K L M N P Q R S IT V W Y
	DEFGHLKL NPQRSTVY	C XIA DEEF H KLMNPQRSTVWYXA
	DEF HIKLMNPORSTV	A DEFGH KL NPQRSTV Y
	DE G NP S	X3 A E G H K L N P R S T
	DEF H LM QRST WY	F H I L M R T W Y
	DEFGHIKLMN QRSTV Y	A DEFGHIKLMN QRSTV Y
	FG IKLM PQRSTVWY	D G
	DEFGH KLMNPQRSTVW	A DEF HIKL ZPQRSTV Y
	DE G IKLMNPQRSTV Y	XA DEF HIKLMN QRST Y
	DEFGHIKLMN Q STV	
	EFGHIKLMNPQRST &	X10
	DEFGH KLMNPQRSTV Y	X11 A
	DEFGHIK MN QRSTV	X12 A
	与行行的 经人工 医有性 医核	C
		to the party county and a formal party of affective and the county of th

Appl. No. 10/693,057 Amdt. dated February 25, 2004 Reply to Notice to File Missing Parts of February 19, 2004

С		¥	(4,6)			С			X(3	51		С.				X/8	.9)				C X/1) C					,	((8/1	2)					С
T	Xi X				.(38)		X1				54	. X1	. X2	:X3				× X7	Х8	, Ya		/-//. X1	X	2 X3	× X4	₩ X5				wish.	w. 3		31 143	
	A A DE E GH KL MNP RSTVW XIA D	A DE GH KLMNPQRSTVW XA	A E G MNPQRST Y X4 A D			日本の日本の日本の日本の日本の日本の日本の日本の日本の日本の日本の日本の日本の日	A DE GH K NPQ STV X1A D	F G H L N Q S T Y XZ A D	A DEFGHIKL N QRSTV Y	X4 A D		X A DEFGHIKLMX ORSTVXY	A DE KL NPQRSTV XA D	ACDEFGHIKLMNPQRSTV YXA D	A DEFGHIKLMNPQRSTVWYXA D	A DEFGHIKL NPQRSTVW X5A D	X A DE GH KLMN QRSTVWY A D	A F H I L P R T V Y A D	A DEF HIKLMN QRSTVWY	i XS	A DEFGHIKLMZPORSTVWY	XA DEF H KLMNPORSTVYYXA D	A DEFGH KL NPORSTV YXA D	A E GH KL NP RST YXX D	F H I L M R · T W Y X A D	A DEFGHIKLMN QRSTV YXX	D G	A DEF HIKL NPQRSTV YX7 A D	A DEF HIKLMN QRST YX8 A D	X9 A D	X10	X111	A D	C
	E F G G H I K L MN P Q R R S T V XX A	FGH L NPQRST WYX	HIKL NP RST	G IKLMNPQRSTV YX5		一 は 一 は 一 は 一 は 一 は 一 は 一 に し で し こ こ こ こ こ こ こ こ こ こ こ こ こ こ こ こ こ	E F G H L K L M N P Q R S T V X1 A	EFGH KL NPQRST YX	т	V X4		HIKLMN QRSTV Y	F H LMNPQRS V Y	G H L N R S T V	G NPQRS	F G K L N P Q	G M N R S	G K L M Q R	V W	S T V		BEGHLKL RPQRSTV Y	LMNPQRS	N P		EFGHIKLMN QRSTV Y	I K L M P Q R S T V W	EFGH KLMNPQRSTVW	E G I K L M N P Q R S T V Y	EFGHIKLMN Q STV	F G H I K L M Z P Q R S	EFGH KLMNPQRSTV Y	EFGHIK MN QRSTV Y	
	DEFGHIKLMNPQRSTV	HIKLMNPOR	DEFGHIKLMNPQRSTV	DHEGHIKL ZEGES >	DE G IKLMNPQRSTV		CDEFGH KLMNPORS V	GHIKLMNPQRST	DEFGH KL N QRST		DEF HIKLMN QRSTV	· · · · · · · · · · · · · · · · · · ·																						

Please replace paragraph [68] beginning at page 18, line 14, with the following:

--[68] The present invention also provides non-naturally-occurring polypeptides comprising an LDL receptor class A domain monomer, wherein the monomer comprises the following sequence:

$$C_aX_{3-15}C_bX_{3-15}C_cX_{6-7}C_d(D,N)X_4C_eX_{4-6}DEX_{2-8}C_f$$
 (SEQ ID NO:219)

wherein C is cysteine, X_{n-m} represents between n and m number of independently selected amino acids, and (D,N) indicates that the position can be either D or N; and wherein C_a - C_c , C_b - C_e and C_d - C_f form disulfide bonds.--

Please replace paragraph [69] beginning at page 18, line 21, with the following:

--[69] In some embodiments, the monomer domain is an LDL receptor class A domain monomer comprising the following sequence:

 $CaX_{6-7}C_{b}X_{4-5}C_{e}X_{6}C_{d}X_{5}C_{e}X_{8-10}C_{f}$

 $\underline{C_{a}X_{6\text{--}7}C_{b}X_{4\text{--}5}C_{c}X_{6}C_{d}X_{5}C_{c}X_{8\text{--}10}C_{f}} (SEQ~ID~NOS:220\text{--}231)$

Appl. No. 10/693,057 Amdt. dated February 25, 2004 Reply to Notice to File Missing Parts of February 19, 2004

c		X(6,7)		. с		,	X(4,5	51		C)	K(6)			С			X(5)	١.		С					X(8	3,10)					С
•	(1 X2 X	3 X4 X	5 X6			X2	Х3	X4		X	1 X	X3	3 X4	X5	Xé			X2	X3	X4	X5			X2		X4 A		X6	X7	X8 A			-, !
1 1 1 1	3 G G H H H I K K K	E F F G H H K K L L	E F H K L		A DEFGH KL ZP	A D GH Z	H K L	ACDEFGHIKLMN	to the second state of the	AF KL	A DEFGH KLMZP	A DEFGHIKLMXP	A DEFGHIKLMXP	A DEFG KLMN	A EF HIKLM P		,	DEFGH KLM	DEFGH1KLM	E F	D E H		H I K L M	G H	DEFGH KL	E	D	E	D E	A DEFGHIKLMNP		,	
F 5	Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q	R R S S T T V V W Y Y	R S T V	X7 A	Q R S T V Y X1 A	Q R S T V Y	Q R S T	Q R S T V	Х5 А	T V Y	Q R S T V W Y		Q R S T V W Y	QRSTVWY	Q R T V W Y			R S T V	R S T V	Q R S T V V Y	ST		R S T V	S T	W Y	R S T	X 5	X6	R S T V W Y	Q R S			
. (_	D	D	D		D !	131											:		D	D			D	E		D E	D E		
f	E E F G G G	E E F G G	F	E : G	E 'G	E G	E G	F	G														F G		G					G	_		; ; :
	э G G	Н	Н	G	Н	ı	Н		H ,													1			H				H	-	Н		1 1
! ! !	K K L L N N N N P P P G R R R S S S T T T	M N P Q R R S T	L	K L M	K L ZPORST>S	KL NPQRSTV	. K NPQRST	N P Q R S T V W	K L M N Q R T V														L M P S T V	N	Q R	ST			L M N P R S	N P Q V	L N Q S		
1	Y						Y	Y		Q.													X1	Y X2	Х3	Y X4	X5	X6					
																						, W	G	D	D F G H	E	D	E	A D E G	A D E H	G	A E H	
																		٠.	•				K L P Q R S	N S	K N Q R S	L S T	*		K L M N P S T W	KLMNPQRS	K L Q S	L M N P Q R T V Y	

Please replace paragraph [71] beginning at page 19, line 7, with the following:

--[71] The present invention also provides non-naturally-occurring polypeptides comprising an EGF domain monomer, wherein the EGF domain monomer comprises the following sequence:

$$C_aX_{3-14}C_bX_{3-7}C_cX_{4-16}C_dX_{1-2}C_eX_{8-23}C_f$$
 (SEQ ID NO:232)

wherein C is cysteine, X_{n-m} represents between n and m number of independently selected amino acids; and

wherein C_a-C_c, C_b-C_e and C_d-C_f form disulfide bonds.--

Please replace paragraph [72] beginning at page 20, line 5, with the following:

--[72] In some embodiments, the monomer domain is an EGF domain monomer comprising the following sequence:

$$C_a X_{4\text{-}6} C_b X_{3\text{-}5} C_c X_{8\text{-}9} C_d X_1 C_e X_{8\text{-}12} C_f \\ \underbrace{(SEQ\ ID\ NOS:233\text{-}322)}_{}$$

Appl. No. 10/693,057 Amdt. dated February 25, 2004 Reply to Notice to File Missing Parts of February 19, 2004

С		X2 Ā		(4,6) X4 A				X1 A) X2	((3,5 X3 A	i)		C X	1 X2 A	Â	X4	X(8, X5 A	X6			•	X(1) X1 A	X	1 X		X4	X5 A		(8/1 X7 A		- marks		****	ana e e e e e e e e e e	C	İ
		DE GH KLMNP RST YX2	GH KLMNPQRSTVW	E G MNPQRST YX4		i		GHK NPQ STV	N Q S T	X3	X4 A		DEFFGHIKLMN QRSTVWYXA	K L N P Q R S T V	CDEFGHIKLMNPQRSTV YX3	DEFGHIKLMNPQRSTVWYX4	DEFGHIKL NPQRSTVW X5	DE GH KLMN QRSTVWYX6	F H I L P R T V Y X7 A	I KLMN QRSTVWY	X9 A	DEFGHIKLMNPQRSTVWY	CEF H KLMNPORSTVVYXA	EFGH KL NPQRSTV YX	S T	T W Y	S T V	D G S S X6 A	S T V	DEF HIKLMN QRST Y.8	Х9	X1 <u>0</u>	X11	XII.		· · · · · · · · · · · · · · · · · · ·
	G .I K L Q R S	DEFGHIKLMNPQRSTV	EFGH L NPQRST W	DEFGHIKL NP RST	FG IKLMNPQRSTV X	•	199	EFGHIKLMNPQRS	H KL NPQRS	G	DEF HIKLMN QRSTV		L MN QRSTV	EF H LMNPQRS V	DEFGH L N RSTV Y	DE G NPQRST	DEFG KL NPQRST		DE G KLM QRST	F HI P R VWY	E H KL Q STV Y		DEFOREXT SPORSTS S	EF HIKLMNPQRS	D E G N P S	DEF H LM QRST WY	DEFGHIKLMN QRSTV Y	FG IKLM PQRST>V	DEFGH KLMNPQRST>V	DE G IKLMRPQRST>. >	DEFGHIKLMN Q STV	EFGHIKLMNPQRST W	DEFGH KLMRPQRSTV V	DEFGHIK MN QRSTV >		
	Α		X3 A		A	X <u>6</u>	- (A .	Α		X4 A	A		, X2		X4	X 5	X6	X 7		Clas		I Y				A S	<u>Y</u>	4 /6	• • • •	<u> </u>					i
	DEFO - KIZZPOR	DEFGHIKLMXPQR	ロ=FGH-KLMNPOR	DEFGHIKLMNPQR	DEFGHIKL NPOR	DE G IKLMZPOR			E GHIKLMNPQ	G H K L		DEF HIKLEZ OR				•												,								
	S T V	S T V	S T V W	S T V	s v y	S T V		V	S	S T	S T V	S T V	ε,								•												•			

Appl. No. 10/693,057 Amdt. dated February 25, 2004 Reply to Notice to File Missing Parts of February 19, 2004

С	V4 V		4,6)		С	v2		X(3,	5)	 Ç.		úá i	~ ~		K(8,9		V7	va			1) C	74.5	72 N	/1 V	4 . V		((8/1 V7						Ć_″
	X1 A DE GH KLMNP RSTVW X1 A	A DE GH KLMNPQRSTVW X3	A E G MNPQRST YX4	X5 A		A DE GH K NPQ STV	H L N Q ST	A DEFGHIKL N QRSTV	. X4		DEFGHIKLMN QRSTVWYX1	A D E KL NPQRSTV	ACDEFGHIKLMNPQRSTV YX3	A DEFGHIKLMNPQRSTVWY	A DEFGHIKL NPQRSTVW	A DE GH KLMN QRSTVWY	F H I L P R T V	A D'EF HIKLMN QRSTVWY		XIA DEFOH-KTWSFORWF>\$>		A)	E F H H I L M R T V Y	A DEFGHIKLMN QRSTV Y	D G	A DEF HIKL NPORSTV Y	A DEF HIKLMN QRST Y		Xi) <u>X1</u>	i X1	2
	DE G G H I K K L L MN N P C R S T T V V X1 X	EFGH L NPQRST WY	GHIKL NP RST	FG IKLMNPQRSTV YX5		HIKLMNPQRSTV	H KL NPQRST Y	Т	DEF HIKLMN QRSTV X4		F HIKLMN QRSTV	EF H LMNPQRS V	E F G H L N RS	DE G NPORST	DEFG KL NPQRST	DE G MN RSTV Y	K L M	P R V	E H K L Q S T V Y			## ## ## ## ## ## ## ## ## ## ## ## ##	1		EFGHIKLMN QRSTV	F G I K L M P Q R S T V W Y	DEFGH KLMNPQRSTVW	DE G IKLMNPQRSTV Y:	DEFGHIKLMN Q STV	EFGHIKLMNPQRST W	DEFGH KLMNPQRSTV Y	O E F G H I K M N Q R S T V Y	
	A DEFG HIKLMANPORSTV Y	A DEFGHIKLMNPQRSTVW	A DEFGHIKLMNPQRSTV	A DEFGHIKL RPORS V	41				Ā F G															•					•				

Please replace paragraph [73] beginning at page 21, line 1, with the following:

--[73] In some embodiments, the EGF domain monomer is fused to a heterologous amino acid sequence. In some embodiments, the monomer binds to a target molecule. In some embodiments, the polypeptide is 45 or fewer amino acids long. In some embodiments, the heterologous amino acid sequence is selected from an affinity peptide (e.g., SKVILF; SEQ ID NO:323), a heterologous LDL receptor class A domain, a heterologous EGF domain, a purification tag, an enzyme (e.g., horseradish peroxidase or alkaline phosphatase), and a reporter protein (e.g., green fluorescent protein or luciferase).--

Please replace paragraph [105] beginning at page 29, line 1, with the following:

--[105] Figure 2 schematically illustrates the alignment of partial amino acid sequence from a variety of the LDL-receptor class A-domains (SEQ ID NOS: 103, 100, 65, 117, 128, 21, 29, 39, 30, 77, 58, 50, and 14, respectively in order of appearance) that include two human LRP1 sequences, two human LRP2 sequences, two human LDLR sequences, two human LDVR sequences, one human LRP3 sequence, one human MAT sequence, a human CO6 sequence, and a human SORL sequence, to demonstrate the conserved cysteines. Consensus = SEO ID NO:324.--

Please replace paragraph [106] beginning at page 29, line 7, with the following:

--[106] Figure 3, panel A schematically illustrates an example of an A-domain. Panel A schematically illustrates conserved amino acids in an A-domain of about 40 amino acids long (SEQ ID NO):325). The conserved cysteine residues are indicated by C, and the negatively charged amino acids are indicated by a circle with a minus ("-") sign. Circles with an "H" indicate hydrophobic residues. Panel B schematically illustrates two folded A-domains

connected via a linker. Panel B also indicates two calcium binding sites, dark circles with Ca⁺², and three disulfide bonds within each folded A-domain for a total of 6 disulfide bonds.--

Please replace paragraph [111] beginning at page 30, line 3, with the following:

--[111] Figure 8 depicts common amino acids in each position of the A domain (SEQ ID NO:326). The percentages above the amino acid positions refer to the percentage of naturally-occurring A domains with the inter-cysteine spacing displayed. Potential amino acid residues in bold depicted under each amino acid position represent common residues at that position. The final six amino acids, depicted as lighter-colored circles, represent linker sequences. The two columns of italicized amino acid residues at positions 2 and 3 of the linker represent amino acid residues that do not occur at that position. Any other amino acid (e.g., A, D, E, G, H, I, K, L, N, P, Q, R, S, T, and V) may be included at these positions.--

Please replace paragraph [112] beginning at page 30, line 11, with the following:

--[112] Figure 9 displays the frequency of occurrence of amino acid residues in naturally-occurring A domains for A domains with the following spacing between cysteines:

CX₆CX₄CX₅CX₈C (SEQ ID NO: 199) (SEQ ID NO:327).--

Please replace paragraph [113] beginning at page 30, line 14, with the following:

--[113] Figure 10 depicts an alignment of A domains (SEQ ID NO: 1-197) (SEQ ID NOS:1-217). At the top and the bottom of the figure, small letters (a-q) indicate conserved residues. The predominant amino acids at these positions and the frequency with which they were observed in native A domains is illustrated at the bottom of the figure.--

Please replace paragraph [118] beginning at page 30, line 26, with the following:

--[118] Figure 15 is a graphical representation of the regions of sequence identity between the sequences of two different selected clones (SEQ ID NOS:328 and 329) and known human sequences from a database. The horizontal bars indicate areas of sequence identity between the sequence of the selected clone and the human sequence and the numbers indicate the exact amino acid numbers that define the region of identity. The vertical arrow depicts an acceptable crossover sequence.--

Please replace paragraph [119] beginning at page 30, line 32, with the following:

--[119] Figure 16 illustrates cell killing induced by CD20-specific A domain monomers. <u>SKVILF = SEQ ID NO:323.</u>--

Please replace paragraph [140] beginning at page 34, line 14, with the following:

--[140] As described *supra*, monomer domains are optionally cysteine rich. Suitable cysteine rich monomer domains include, e.g., the LDL receptor class A domain ("Adomain") or the EGF-like domain. The monomer domains can also have a cluster of negatively charged residues. Optionally, the monomer domains contain a repeated sequence, such as YWTD (SEQ ID NO: 198) (SEQ ID NO:218) as found in the β-Propeller domain.--

Please replace paragraph [144] beginning at page 35, line 17, with the following:

--[144] Exemplary A domain sequences and consensus sequences are depicted in Figures 2, 3 and 8. Figure 9 displays location and occurrence of residues in A domains with the following spacing between cysteines. In addition, Figure 10 depicts a number of A domains and

Appl. No. 10/693,057 Amdt. dated February 25, 2004

Reply to Notice to File Missing Parts of February 19, 2004

provides a listing of conserved amino acids. One typical consensus sequence useful to identify A domains is the following: C-[VILMA]-X₍₅₎-C-[DNH]-X₍₃₎-[DENQHT]-C-X_(3,4)-[STADE]-[DEH]-[DE]-X_(1,5)-C (SEQ ID NO: 200) (SEQ ID NO: 330), where the residues in brackets indicate possible residues at one position. "X_(#)" indicates number of residues. These residues can be any amino acid residue. Parentheticals containing two numbers refers to the range of amino acids that can occupy that position (e.g., "[DE]-X_(1,5)-C" means that the amino acids DE are followed by 1, 2, 3, 4, or 5 residues, followed by C). This consensus sequence only represents the portion of the A domain beginning at the third cysteine. A second consensus is as follows: C-X₍₃₋₁₅₎-C-X₍₄₋₁₅₎-C-X₍₆₋₇₎-C-[N,D]-X₍₃₎-[D,E,N,Q,H,S,T]-C-X₍₄₋₆₎-D-E-X₍₂₋₈₎-C (SEQ ID NO: 201) (SEQ ID NO: 331). The second consensus predicts amino acid residues spanning all six cysteine residues. In some embodiments, A domain variants comprise sequences substantially identical to any of the above-described sequences.--

Please replace paragraph [145] beginning at page 35, line 32, with the following:

--[145] Additional exemplary A domains include the following sequence:

$$C_a X_{3\text{-}15} C_b X_{3\text{-}15} C_c X_{6\text{-}7} C_d (D,N) X_4 C_e X_{4\text{-}6} DEX_{2\text{-}8} C_f \\ \underline{(SEQ\ ID\ NO:219)}$$

wherein C is cysteine, X_{n-m} represents between n and m number of independently selected amino acids, and (D,N) indicates that the position can be either D or N; and wherein C_a - C_c , C_b - C_e and C_d - C_f form disulfide bonds.--

Please replace paragraph [146] beginning at page 36, line 4, with the following:

--[146] In some embodiments, the monomer domain is an LDL receptor class A domain monomer comprising the following sequence:

 $\begin{array}{l} C_{11}C_{12}C_{13}C_{14}C_{15}C_{14}C_{15}C_{14}C_{15$

Appl. No. 10/693,057 Amdt. dated February 25, 2004 Reply to Notice to File Missing Parts of February 19, 2004

С				X(6	.7)				С				X(4	.5)		С				X((6)			С			X(5)		С					X(8,10)				С
		X2 A	Х3	X	4 X						K1	X2		X4 A		 !	X			K3			X6	,	X1	X2 A			Х5		X1 A	X2	X3 A	X4 A				X8 A			
	D E F G H	CDE GHI	DEFGH	DEFGH	F	E F	≣ = -			E F C) = 3	D G H	E G H	CDEFGH			F	D F G H	6 F H	DEFGH	DEFGHI	D E F. G	E F H I		D	D E F G H	DEFGHI	DEF HI	D E H		D E G H I	D G H	D F G H	E G	,	E.	F G H I	DEFGH!			
	KLMNPQR	KLMNPQR	K NPQR	K L M N Q R	L M	L 1 N F 1 C	N 0 0			in in	2 2 2	N Q R	KL N QR	K L M N Q R		1.	K L	L N P G R	L N F	KLMNPQR	KLMNPQR	K L M N Q R	K L M P Q R		: : N :	K L M N Q R	K L M N Q R	KL NPQR	N Q		K L M P Q R	N Q		L M			K L M N Q R	KLMNPQR			j
	S T V	S T V W Y X2 A	S T V W Y	S T Y		' \ ' \	Γ /	X7	:	,	Γ / Y	S T V Y X2	S T	S T V	X5 A		'T 'V 'Y	\$ V W Y	٦ ١ /	τ V	S V V Y	S T V W Y	T W Y	:		S T V W Y	S T V W Y	S T V W Y	ST		٧	S T Y X2		S T	X5	X6	S T V W Y X7 A		X9 A		
	DEFGH	D E G H	D F G	DEFGH	E	F		E G	:	:6		D E G	D E G H	DEFGH	D E G H	A Company of the Company														2	D F G	D	G H		D	E	E G H	D E G	E D.		5
:	K L NP RST	LNPRST	KL NPQRST	K MN RST	K L N P C	: !		K L M R S T	***************************************		<- v - Q - Q - S	IKL RPQRST	. IK NPORST	. I K L N P Q R S T	KLMN QR T																LM P ST	N	Q R	ST			L M N P R S	N P Q	L N Q S		1.000
			Y	V		. /	/ //	v		() ()	/ // 	v	Y	V W Y	V 	American															X1	Y X2 D	X3	Y X4 A	X5 D	X6	X7 Ā D	V Y X8 A	X9 A D	X1())
																					٠												F G H	Ε	•	E	E G	H	E G H I	E H I	
																															K L P Q R S	N S	K N QRS	L S			K L M N P S	KLMXPQRS	K L Q STV	LMNPQR	Ġ.
						٠																											W Y	Т	,		T W 	. 1	Т V _Y	T V Y_	

The table above indicates alternative amino acid residues at each position of the LDL receptor class A monomer domain. For example, there can be either 6 or 7 amino acids between cysteine C1 and cysteine C2. The upper left box of the table indicates alternative amino acid residues at each position if there are 6 amino acids between C1 and C2. The bottom left box in the table

indicates alternative amino acid residues if there are seven amino acids between C1 and C2. In all cases, the amino acid for one position (e.g., X1) is selected independently of the amino acids selected for remaining positions (e.g., X2, X3, etc.).

Please replace paragraph [148] beginning at page 37, line 21, with the following:

--[148] Another exemplary monomer domain suitable for use in the practice of the present invention is the C2 domain. C2 monomer domains are polypeptides containing a compact β-sandwich composed of two, four-stranded β-sheets, where loops at the "top" of the domain and loops at the "bottom" of the domain connect the eight β-strands. C2 monomer domains may be divided into two subclasses, namely C2 monomer domains with topology I (synaptotagmin-like topology) and topology II (cytosolic phospholipase A2-like topology), respectively. C2 monomer domains with topology I contains three loops at the "top" of the molecule (all of which are Ca2+ binding loops), whereas C2 monomer domains with topology II contain four loops at the "top" of the molecule (out of which only three are Ca2+ binding loops). The structure of C2 monomer domains have been reviewed by Rizo and Südhof, J. Biol. Chem. 273;15879-15882 (1998) and by Cho, J. Biol. Chem. 276;32407-32410 (2001). The terms "loop region 1". "loop region 2" and "loop region 3" refer to the Ca²⁺ binding loop regions located at the "top" of the molecule. This nomenclature, which is used to distinguish the three Ca2+ binding loops located at the "top" of the molecule from the non-Ca2+ binding loops (mainly located at the "bottom" of the molecule) is widely used and recognized in the literature. See Rizo and Südhof, J. Biol. Chem. 273;15879-15882 (1998). Loop regions 1, 2, and 3 represent target binding regions and thus can be varied to modulate binding specificity and affinity. The remaining portions of the C2 domain can be maintained without alteration if desired. Some exemplary C2 domains are substantially identical to the following sequence (SEQ-ID NO: 202) (SEQ ID NO:332):

PATENT

Appl. No. 10/693,057 Amdt. dated February 25, 2004 Reply to Notice to File Missing Parts of February 19, 2004

Residues 1-16, 29-48, 54-77 and 86-123 constitute positions located outside loop regions 1, 2 and 3 and residues 17-28, 49-53 and 78-85 constitute the loop regions 1, 2 and 3, respectively.--

Please replace paragraph [151] beginning at page 39, line 4, with the following:

--[151] Exemplary EGF monomer domains include the sequence:

$$C_aX_{3-14}C_bX_{3-7}C_cX_{4-16}C_dX_{1-2}C_eX_{8-23}C_f$$
 (SEQ ID NO:232)

wherein C is cysteine, X_{n-m} represents between n and m number of independently selected amino acids; and

wherein C_a-C_c, C_b-C_e and C_d-C_f form disulfide bonds.--

Please replace paragraph [152] beginning at page 39, line 9, with the following:

--[152] In some embodiments, the monomer domain is an EGF domain monomer comprising the following sequence:

 $C_aX_{4-6}C_bX_{3-5}C_cX_{8-9}C_dX_1C_eX_{8-12}C_f$ (SEQ ID NOS:233-322) wherein X is defined as follows:

Appl. No. 10/693,057 Amdt. dated February 25, 2004 Reply to Notice to File Missing Parts of February 19, 2004

C X(4,6) X1 X2 X3 X4	C X(3,5) C X(8,9) C X(1) C X(8/12) X1 X2 X3 X1 X2 X3 X4 X5 X6 X7 X8 X1 X1 X2 X3 X4 X5 X6 X7 X8	C
A A A A D D D E E E E F G G G G H H H I K K L L L M M M N N N N N P P P P Q Q Q R R R R S S S S T T T T V V V V Y X1 X2 X3 X4 X5 A A A A	A A A A A A A A A A A A A A A A A A A	
D D D E E E E F F F F F F F F F F F F F	D D D D D D D D D D D D D D D D D D D	
D D D D D D D D E E E E E E E E E E E E	C D D D D D D D D D D D D D D D D D D D	

Appl. No. 10/693,057 Amdt. dated February 25, 2004 Reply to Notice to File Missing Parts of February 19, 2004

С	A DEFG	Ē	A D E G	A E	-	•	С	A D E G	X2 F G	G				DEFG	D E	CDEFG	X4 A D E F G	D E F G	X6 A D E	F	D E F			D E F	•	F	A D E F G	A E G	F	A DEFG	X6 D	A D E F	X8 A D E F		4			C
*	I K L N P Q R S T V W X1	N P	K L M N P Q R S T V W	M N P Q R S T Y X4			· · · · · ·	K N P Q S T V		I K L N QRSTV				KLMN QRSTVWYX	R S T V	I K L M N P Q R S T V Y X3	I K L M N P Q R S T V W Y X4	R S T V W	KLMN QRSTVWYX6	I L P R T V	HIKLMN QRSTVWYX8	-		- KLMNPQRSTVXY		KLMNPQRSTVVY	Q R S T V Y	K L NP RST Y	T W Y	I K L M N Q R S T V Y X 5	S	N P Q R S T V Y	I K L M N Q R S T Y	X9 A	X10) <u>X11</u>	# X12	
	DE G IKL QRST	DEFGHI	EFGH L NPQRS	DEFGHIKL XP RS	FG KLMZPQRS		3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	DEFOI-K-MZPORST	DEFGH KL NPQRS	G	DEF HIKLMN ORS			D F HIKLMN QRST	DEF. H LMNPQRS	DEFGH L N . RST	DE G NPQRS	DEFG KL ZPG	DE G MN RS	DE G KLM QR	P R	E H. K L				DEFOH-KI ZPOR	DEF HIKLMRPOR	E G N P	EF H LM QR	EFGH_KLMZ GR	G IKLM POR	GH KLMNPOR	S T	FGHIKLMN Q STV	I K L M N P Q R S T	N P Q R	I K M N Q R S	
	X1 A					X6 A		Α		X3			1-,-	Y 	Υ.	Y	-	99 - 111	. Y		Y	y	~ ~~		-	Υ			Y	Υ	Υ		Υ_		ala (. i	Υ	Υ	
441	DEFG IKLMRPORS	F G H I K L	E F G H L K L Z Z P Q R		EFGHIKL ZPOR	Ε		PEGH KLMPPOR	HIKLMNPQR	E F G H	G H Q	HIKLMN OR																										
	Y	Y	V W	т У	V 'Y	Y	٠.	V _Y	٧	Y	٧	٧																										

Please replace paragraph [209] beginning at page 60, line 25, with the following:

--[209] One example where the use of peptide linkers is widespread is for production of single-chain antibodies where the variable regions of a light chain (V_L) and a heavy chain (V_H) are joined through an artificial linker, and a large number of publications exist within this particular field. A widely used peptide linker is a 15mer consisting of three repeats of a Gly-Gly-Gly-Ser (SEQ ID NO: 240) (SEQ ID NO:333) amino acid sequence ((Gly₄Ser)₃) (SEQ ID NO:334). Other linkers have been used, and phage display technology, as well as, selective infective phage technology has been used to diversify and select appropriate linker sequences (Tang *et al.* (1996), *J. Biol. Chem.* 271, 15682-15686; Hennecke *et al.* (1998), *Protein Eng.* 11, 405-410). Peptide linkers have been used to connect individual chains in hetero- and homo-dimeric proteins such as the T-cell receptor, the lambda Cro repressor, the P22 phage Arc repressor, IL-12, TSH, FSH, IL-5, and interferon-γ. Peptide linkers have also been used to create fusion polypeptides. Various linkers have been used and in the case of the Arc repressor phage display has been used to optimize the linker length and composition for increased stability of the single-chain protein (Robinson and Sauer (1998), *Proc. Natl. Acad. Sci. USA* 95, 5929-5934).--

Please replace paragraph [211] beginning at page 61, line 10, with the following:

--[211] Still another way of obtaining a suitable linker is by optimizing a simple linker, e.g. (Gly₄Ser)_n (SEQ ID NO: 240) (SEQ ID NO:335), through random mutagenesis.--

Please replace paragraph [212] beginning at page 61, line 12, with the following:

--[212] As mentioned above, it is generally preferred that the peptide linker possess at least some flexibility. Accordingly, in some embodiments, the peptide linker contains 1-25 glycine residues (SEQ ID NO:336), 5-20 glycine residues (SEQ ID NO:337), 5-15 glycine residues (SEQ ID NO:338) or 8-12 glycine residues (SEQ ID NO:339). The peptide linker will

Appl. No. 10/693,057 Amdt. dated February 25, 2004

Reply to Notice to File Missing Parts of February 19, 2004

typically contain at least 50% glycine residues, such as at least 75% glycine residues. In some embodiments of the invention, the peptide linker comprises glycine residues only.--

Please replace paragraph [213] beginning at page 61, line 18, with the following:

--[213] The peptide linker may, in addition to the glycine residues, comprise other residues, in particular residues selected from the group consisting of Ser, Ala and Thr, in particular Ser. Thus, one example of a specific peptide linker includes a peptide linker having the amino acid sequence Glyx-Xaa-Glyy-Xaa-Glyz (SEQ ID NO: 203), wherein each Xaa is independently selected from the group consisting Ala, Val, Leu, Ile, Met, Phe, Trp, Pro, Gly, Ser, Thr, Cys, Tyr, Asn, Gln, Lys, Arg, His, Asp and Glu, and wherein x, y and z are each integers in the range from 1-5 (SEQ ID NO:340). In some embodiments, each Xaa is independently selected from the group consisting of Ser, Ala and Thr (SEQ ID NO:341), in particular Ser (SEQ ID NO:342). More particularly, the peptide linker has the amino acid sequence Gly-Gly-Gly-Xaa-Gly-Gly-Gly-Gly-Gly-Gly-Wellow (SEQ ID NO: 204), wherein each Xaa is independently selected from the group consisting Ala, Val, Leu, Ile, Met, Phe, Trp, Pro, Gly, Ser, Thr, Cys, Tyr, Asn, Gln, Lys, Arg, His, Asp and Glu (SEQ ID NO:343). In some embodiments, each Xaa is independently selected from the group consisting of Ser, Ala and Thr (SEQ ID NO:344), in particular Ser (SEQ ID NO:345).--

Please replace paragraph [217] beginning at page 62, line 20, with the following:

--[217] In a further embodiment, the peptide linker comprises glycine residues and cysteine residue, such as glycine residues and cysteine residues only. Typically, only one cysteine residue will be included per peptide linker. Thus, one example of a specific peptide linker comprising a cysteine residue, includes a peptide linker having the amino acid sequence Glyn-Cys-Glym (SEQ ID NO: 205), wherein n and m are each integers from 1-12 (SEQ ID

NO:348), e.g., from 3-9, from 4-8, or from 4-7. More particularly, the peptide linker may have the amino acid sequence GGGGG-C-GGGGG (SEQ ID NO: 206) (SEQ ID NO:349).--

Please replace paragraph [222] beginning at page 63, line 20, with the following:

--[222] A specific example of a peptide linker comprising an *in vivo* N-glycosylation site is a peptide linker having the amino acid sequence Gly_n-Asn-Xaa-Ser/Thr-Gly_m (SEQ ID NO: 209) (SEQ ID NO: 350), preferably Gly_n-Asn-Xaa-Thr-Gly_m (SEQ ID NO: 210) (SEQ ID NO: 351), wherein Xaa is any amino acid residue except proline, and wherein n and m are each integers in the range from 1-8, preferably in the range from 2-5.--

Please replace paragraph [226] beginning at page 64, line 12, with the following:

--[226] A linker can be a native or synthetic linker sequence. An exemplary native linker includes, e.g., the sequence between the last cysteine of a first LDL receptor A domain and the first cysteine of a second LDL receptor A domain can be used as a linker sequence. Analysis of various A domain linkages reveals that native linkers range from at least 3 amino acids to fewer than 20 amino acids, e.g., 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 amino acids long. However, those of skill in the art will recognize that longer or shorter linker sequences can be used. An exemplary A domain linker sequence is depicted in Figure 8. In some embodiments, the linker is a 6-mer of the following sequence A₁A₂A₃A₄A₅A₆ (SEQ ID NO: 244) (SEQ ID NO:352), wherein A₁ is selected from the amino acids A, P, T, Q, E and K; A₂ and A₃ are any amino acid except C, F, Y, W, or M; A₄ is selected from the amino acids S, G and R; A₅ is selected from the amino acids H, P, and R; and A₆ is the amino acid, T.--

Please replace paragraph [334] beginning at page 98, line 11, with the following:

--[334] The following list (SEQ ID NOS:353-357) provides sequences of monomer domains analyzed in this example.

IG156 CLSSEFQCQSSGRCIPLAWVCDGDNDCRDDSDEKSCKPRT
RBCA CRSSQFQCNDSRICIPGRWRCDGDNDCQDGSDETGCGDSHILPFSTPGPST
RBCB CPAGEFPCKNGQCLPVTWLCDGVNDCLDGSDEKGCGRPGPGATSAPAA
RBC11 CPPDEFPCKNGQCIPQDWLCDGVNDCLDGSDEKDCGRPGPGATSAPAA
CSA-A8 CGAGOFPCKNGHCLPLNLLCDGVNDCEDNSDEPSELCKALT--

Please replace paragraph [336] beginning at page 98, line 22, with the following:

--[336] Anti-6xHis (SEQ ID NO:358) antibody was immobilized by hydrophobic interaction to a 96-well plate (Nunc). Serial dilutions of serum from each blood sample were incubated with the immobilized antibody for 3 hours. Plates were washed to remove unbound protein and probed with α -HA-HRP to detect monomer.--

Please replace paragraph [338] beginning at page 98, line 29, with the following:

--[338] One monkey was injected subcutaneously per pool, at a dose of 0.25 mg/kg/monomer in 2.5 mL total volume in saline. Blood samples were drawn at 24, 48, 96, and 120 hours. Anti-6xHis (SEQ ID NO:358) antibody was immobilized by hydrophobic interaction to a 96-well plate (Nunc). Serial dilutions of serum from each blood sample were incubated with the immobilized antibody for 3 hours. Plates were washed to remove unbound protein and separately probed with α-HA-HRP, α-FLAG-HRP, α-ETag-HRP, andα-myc-HRP to detect the monomer.--

Please replace paragraph [344] beginning at page 99, line 29, with the following:

--[344] A library of DNA sequences encoding monomeric C2 domains is created by assembly PCR as described in Stemmer *et al.*, *Gene* 164, 49-53 (1995). The oligonucleotides used in this PCR reaction are (SEQ ID NOS: 211-223 SEQ ID NOS:359-371, respectively, in order of appearance):

- 5'-acactgcaatcgcgccttacggctCCCGGGCGGATCCtcccataagttca
- 5'-agctaccaaagtgacannknnknnknnknnknnknnknnknnknnknnknnkccatacgtcgaattgttca t
- 5'-agctaccaaagtgacaaaaggtgcttttggtgatatgttggatactccagatccatacgtcgaattgttca t
- 5'-taggaagagaacacgtcattttnnknnknnkattaaccctgtttggaacgagacctttgagt
- $\verb|5'-taggaagaagaacacgtcattttaataatgatattaaccctgtttggaacgagacctttgagt|\\$
- 5'-ttggaaatcacctaatgnnknnknnknnknnknnknnknnkactctaggtacagcaa
- 5'-ttggaaatcaccctaatggatgcaaattatgttatggacgaaactctaggtacagcaa
- 5'-aagaaggaagtcccatttattttcaatcaagttactgaaatggtcttagagatgtccctt
- 5'-tgtcactttggtagctcttaacacaactacagtgaacttatgggaGGA
- 5'-acgtgttctcttcctagaatctggagttgtactgatgaacaattcgacgta
- 5'-attagggtgatttccaaaacattttcttgattaggatctaatataaactcaaaggtctcgtt
- 5'-atgggacttccttctttctcccactttcattgaagatacagtaaacgttgctgtacctagagt
- 5'-gaccgatagcttgccgattgcagtgtGGCCACAGAGGCCTCGAGaacttcaagggacatctctaaga--

Please replace paragraph [349] beginning at page 100, line 31, with the following:

--[349] The oligonucleotides used in this PCR reaction are (SEQ-ID NOS: 224-225 SEQ ID NOS:372 and 373, respectively, in order of appearance):

- 5'-acactqcaatcqcqccttacqqctCAGqtqCTGqtggttcccataagttcactgta

Please replace paragraph [350] beginning at page 100, line 37, with the following:

--[350] PCR fragments are then digested with AlwNI, digestion products are separated on 1.5% agarose gel and C2 domain fragments are purified from the gel. Subsequently, PCR fragments are multimerized by DNA ligation in the presence of stop fragments. The stop fragments are listed below:

Stop1 (SEQ-ID-NO:226) (SEQ ID NO:374):

5'-gaattcaacgctactaccattagtagaattgatgccaccttttcagctcgcgccccaaat gaaaaaatggtcaaactaaatctactcgttcgcagaattgggaatcaactgttacatggaatgaaacttccagacac cgtactttatgaatatttatgacgattccgaggcgcccggactacccgtatgatgttccggattatgccccgggatccccgggattccaggtgctg-3' (digested with EcoRI and AlwNI).

Stop2 (SEQ ID NO:227) (SEQ ID NO:375):

5'-caggtgctgcactcgaggccactgcggccgcatattaacgtagatttttcctccc aacgtcctgactggtataatgagccagttcttaaaatcgcataaccagtacatggtgattaaagttgaaattaaaccgttcaagagctttgttacgttgatttgggtaatgaagctt-3' (digested with AlwNI and HindIII).--

Please replace paragraph [352] beginning at page 101, line 11, with the following:

--[352] Multimers are separated on 1% agarose gel and DNA fragments corresponding to stop1-C2-C2-stop2 Stop1-C2-C2-Stop2 are purified from the gel. Stop1-C2-C2-stop2 Stop1-C2-C2-Stop2 fragments are PCR amplified using primers 5' aattcaacgctactaccat-3' (SEQ ID NO:242) (SEQ ID NO:376) and 5'-agcttcattacccaaatcaac-3' (SEQ ID NO:243) (SEQ ID NO:377) and subsequently digested with BamHI and XhoI. Optionally, the polynucleotides encoding the multimers can be put through a further round of affinity screening (e.g., FACS analysis as described above).--

Please replace paragraph [355] beginning at page 101, line 24, with the following:

--[355] A library of DNA sequences encoding monomeric A domains is created by assembly PCR as described in Stemmer *et al.*, *Gene* 164, 49-53 (1995). The oligonucleotides used in this PCR reaction are (SEQ ID NOS: 228-235 SEQ ID NOS:378-385, respectively, in order of appearance):

- $\verb| 5'-CACTATGCATGGACTCAGTGTTCCGATAAGGGCACACGGTGCCTACCCGTATGATGTTCCGGATTATGCC| \\ \texttt| CCGGGCAGTA| \\ | CCGGGCAGT$
- 5'-CGCCGTCGCATMSCMAGYKCNSAGRAATACAWYGGCCGYTWYYGCACBKAAATTSGYYAGVCNSACAGGTACTGCCCGGGGCAT
- 5'-CGCCGTCGCATMSCMATKCCNSAGRAATACAWYGGCCGYTWYYGCACBKAAATTSGYYAGVCNSACAGGTACTGCCCGGGGCAT
- $\verb| 5 | \texttt{ATGCGACGGCGWWRATGATTGTSVAGATGGTAGCGATGAAVWGRRTTGTVMAVNMVNMVGCCVTACGGGCTCT}| \\ | CGGCCTCT| \\ | CGGCTCT| \\ | CGGCCTCT| \\ | CGGCCTCT$

- 5'-ATGCGACGGCGWWCCGGATTGTSVAGATGGTAGCGATGAAVWGRRTTGTVMAVNMVNMVGCCVTACGGGCTCGGCCTCT
- 5'-ATGCGACGGCGWWRATGATTGTSVAGATAACAGCGATGAAVWGRRTTGTVMAVNMVNMVGCCVTACGGGCTCT
- 5'-ATGCGACGGCGWWCCGGATTGTSVAGATAACAGCGATGAAVWGRRTTGTVMAVNMVNMVGCCVTACGGGCTCT
- $\tt 5'-TCCTGGTAGTACTTATCTACTACTATTTGTCTGTGTCTGGGTTCCTAACGGTTCGGCCACAGAGGCCGGTA$

where R=A/G, Y=C/T, M=A/C, K=G/T, S=C/G, W=A/T, B=C/G/T, D=A/G/T, H=A/C/T, V=A/C/G, and N=A/C/G/T.--

Please replace paragraph [359] beginning at page 102, line 19, with the following:

--[359] The oligonucleotides used in this PCR reaction are:

5'-aagcctcagcgaccgaa (SEQ-ID-NO: 236) (SEQ ID NO: 386)

5'-agcccaataggaacccat (SEQ-ID-NO: 237) (SEQ ID NO:387)--

Please replace paragraph [360] beginning at page 102, line 22, with the following:

--[360] PCR fragments are digested with AlwNI and BgII. Digestion products are separated on 3% agarose gel and A domain fragments are purified from the gel. PCR fragments are multimerized by DNA ligation in the presence of the following stop fragments: Stop1 (SEQ ID NO: 238) (SEQ ID NO: 388):

5'-gaattcaacgctactaccattagtagaattgatgccaccttttcagctcgcgccccaaatgaaaaaatggt caaactaaatctactcgttcgcagaattgggaatcaactgttacatggaatgaaacttccagacaccgtactttatg aatatttatgacgattccgaggcgcgcccggactacccgtatgatgttccggattatgccccgggcggatccagtac ctq-3'

(digested with EcoRI and ALwNI)
Stop2 (SEQ ID NO: 239) (SEQ ID NO: 389):

5'-gccctacgggcctcgaggcacctggtgcggccgcatattaacgtagatttttcctcccaacgtcctgactg gtataatgagccagttcttaaaatcgcataaccagtacatggtgattaaagttgaaattaaaccgtctcaagagctttgttacgttgatttgggtaatgaagctt-3'

(digested with BglI and HindIII).--

Please replace paragraph [362] beginning at page 103, line 1, with the following:

--[362] Multimers are separated on 1% agarose gel and DNA fragments corresponding to stop1-A-A-A-stop2 Stop1-A-A-A-stop2 Stop1-A-A-A-Stop2 are purified from the gel. Stop1-A-A-A-Stop2 fragments are subsequently PCR amplified using primers 5'-agcttcattacccaaatcaac-3' (SEQ ID NO:390) and 5' aattcaacgctactaccat-3' (SEQ ID NO:391) and subsequently digested with XmaI and SfiI. Selected polynucleotides are then cloned into a phage expression system and tested for affinity for the target protein.--

Please replace paragraph [367] beginning at page 103, line 24, with the following:

--[367] Clones which showed differential binding were sequenced (Table 1) and cloned into expression vectors with SKVILF (SEQ ID NO:323) peptides fused N- and C-terminally. Protein was produced and purified according to standard methods.--

Please replace paragraph [368] and Table 1 beginning at page 103, line 27, with the following:

--[368] Raji or Daudi cells were incubated in fresh RPMI medium supplemented with 10% FBS in the presence or absence of purified monomers for 6 hours at 37°C. Dead cells were stained with trypan blue and counted visually using a hemocytometer (Figure 16).

Table 1: CD20 binding sequences (SEQ ID NOS:392-406)

- 2 CLPDEFQCRSTGICIPLAWRCDGVNDCQDDSDETNCRATGRT
- 3 CLPGEFRCRGTSICIPPSWVCDGVDDCGDGSDEALEHCGDSHILPFSTPGPST
- 4 COPNEFPCGSTGLCVPREWLCDGVDDCQDGSDEPDCGDSHILPFSTPGPST
- 5 CLPGEFRCRGTSICIPPSWVCDGVDDCGDGSDEALEHCGDSHILPFSTPGPST
- 6 CRSGEFKCHGTRPCVPQRWVCDGDDDCVDGSDEKSCETPARR
- 7 CRSSQFKCHNTRPCIPGRWVCDGVNDCLDGSDEANCRRAARR
- 8 CLPERFQCAVPGYCIPLPGVCDGVNDCQEDSDEPNCRAPGLR
- 9 CRRNEFRCKSGHCVPQPLVCDGVRDCEDNSDEPSCGRPGPGATSAPAA

PATENT

Appl. No. 10/693,057 Amdt. dated February 25, 2004 Reply to Notice to File Missing Parts of February 19, 2004

- 10 CRAGEFPCKNGQCLPVTWLCDGVNDCLDGSDEKGCGRPGPGATSAPAA
- 11 CPSNEFTCKSGHCVPQPFVCDGVPDCEDNSDETSCGRPGPGATSAPAA
- 14 CRASEFPCRGTGTCIPRHWLCDGENDCADSSDEKDCGRPGPGATSAPAA
- 15 CPPDEFRCKSYKRCVPLÁFVCDGVDDCEDGSDEEGCGRPGPGATSAPAA
- 1 CLPDEFOCRSTGICIPLAWRCDGVNDCQDDSDETNCRATGRT
- 6 CPAGEFQCGNGQCIPATWLCDGVNDCLDNSDETGCSQDPEFHKV
- CC3 CPASQFKCHNTRTCIPRRWVCDGVNDCLDGSDEANCRRAAPT--

Please replace paragraph [374] and Table 2 beginning at page 104, line 36, with the following:

--[374] Positive clones were genetically fused to create direct homodimers, with and without insertion of a 12 amino-acid repeated Gly-Gly-Ser linker (SEQ ID NO:407) between the domains, using standard molecular biology techniques, and were cloned into an expression vector. Protein was produced and purified using standard techniques. Protein was assayed for its ability to mimic natural TPO activity in a TF1 cell proliferation assay (Figure 18).

Table 2: TPO-R Binding Sequences (SEQ ID NOS:408-411)

T4690 (TPO1) CHSTGEFRCRSSGICVSPTWVCDGENDCLDGSDEASCTAAGPT
T5 (TPO2) CPPSEFRCNSGQCIPREWRCDGDNDCADNSDEESCSAPASEPPGSLSLQ
T2 (TPO9) CLPSEFRCSSGHCIPRRWRCDGEPDCQDGSDEANCGTSEHTSLQ

12 (1FO9) CHPSERRESSGRETERRAREDGEFDEQUESDEARCGISERTSLQ

T1 (TPO10) CQSNEFQCHNYNICLPRPWVCDGVNDCPDGSDEEGCSAPASEPPGSLSLQ--

Please replace paragraph [382] and Table 3 beginning at page 106, line 5, with the following:

--[382] Phage were selected on serial dilutions 2 additional times. Individual clones were sequenced (Table 3)

Table 3: IgE-Binding Monomer Sequences

IGE-1

CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSLSLQ (SEQ ID NO:412)

Walked Dimers

1

CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSL

CQPDQFRCSSGRCLSREWLCDGEDDCEDDSDETDCPTRTSLQ (SEQ ID NO:413)

CPANEFOCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSL

CLPSQFPCDSGNCLPLTWLCDGVDDCGDNSDEEDCSAPASEPPGSLSLQ (SEQ ID NO:414)

```
Appl. No. 10/693,057
Amdt. dated February 25, 2004
Reply to Notice to File Missing Parts of February 19, 2004
CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSL
CRANQFPCDNGNCLPQPWRCDGDNDCVDGSDETSCEAPAHTSLQ (SEQ ID NO:415)
CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSL
CAPNEFQCRDNNTCLPEDWRCDGEDDCADNSDEANCTTPGPTSLQ (SEQ ID NO:416)
CPANEFQCRNSSTCIPRRWLCDGEDDCEDGSDEASDECSAPASEPPGSL
CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSLSLQ (SEQ ID NO:417)
CGSGQFPCGSGHCVPLNWVCDGVDDCGDDSDETDCKAHT
CPANEFOCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSLSLQ (SEQ ID NO:418)
CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSL
CGADQFPCSSGHCIPLPWVCDGEDDCADGSDEADCRGTEPTSLQ (SEQ ID NO:419)
CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSL
CAPSOFRCGNGRCIPRSWRCDGEDDCADDSDEENCSAPASEPPGSLSLQ (SEQ ID NO:420)
RVWRRLVGS
CRPNQFTCKSSETCIPAHWRCDGDDDCGDGSDEADCETRT
CPANEFOCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSLSLQ (SEQ ID NO:421)
10
CPANEFOCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSL
COSSOFPCHDYEICLPATLLCDGVDDCLDGSDETNCAKPTSLQ (SEQ ID NO:422)
CPANEFOCRNSSTCIPRRWLCDGDDDCGDGSDEPGCSAPASEPPGSL
CPPGEFPCGNGRSVPLTWLCDGVDDCGDNSDETGCETTGRTSLQ (SEQ ID NO:423)
CGSNQFPCENGNCVPLGWGCDGVNDCQDNSDESLATCGRPGPGATSAPAA
CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSLSLQ (SEQ ID NO:424)
CPSGQFPCDNGHCIPRRWLCDGEDDCPDGSDEAQVCQQRT
CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSLSLQ (SEQ ID NO:425)
CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSLSLQ
ALLCDGVDDCRDGSDESALCEEHT
CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSL|SLQ (SEQ ID NO:426)
16
CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDEPGCSAPASEPPGSL
CRRAEFTCRNGSCLPVPWLCDAENDCPDGSDEPDCGSPARRSLQ (SEQ ID NO:427)
CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDEPGCSAPASEPPGSL
CPPDQFRCKNGRCIPRHLVCDGDDDCGDDSDEAGCQTRTSLQ (SEQ ID NO:428)
CPANEFOCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSL
CEPGOFOCNNNDTCVSPPWLCDADRDCGRSDERPPHCATPELTSLQ (SEQ ID NO:429)
CPAGQFRCENGRCLPPPWRCDGVNDCEDNSDEAGCGDSHILPFSTPGPST
CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSLSLQ (SEQ ID NO:430)
```

PATENT

Appl. No. 10/693,057 Amdt. dated February 25, 2004 Reply to Notice to File Missing Parts of February 19, 2004

```
CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDEPGCSAPASEPPGSL

CLSSQFRCENGQCIPLTWGCDGDDDCQDGSDETNCPTRTSLQ (SEQ ID NO:431)

26

CPANEFQCRNSSTCIPRRWLCDGDDDCWDGSDETGCGSPVPT

CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSLSLQ (SEQ ID NO:432)

27 (13)

CGSNQFPCENGNCVPLGWGCDGVNDCQDNSDESLATCGRPGPGATSAPAA

CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSLSLQ (SEQ ID NO:424)

30

CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDEPGCSAPASEPPGSL

CAASQFRCNNNSRCLPPPLGCDGVDDCGDGSDEPGCSAPASEPPGSL

CAASQFRCNNNSRCLPPPLGCDGVDDCGDGSDETGCSAPASEPPGSL

CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSL

CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSL

CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSL

CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSL

CPANEFQCRNSSTCIPRRWLCDGEDDCGDGSDETGCSAPASEPPGSL

CPANEFQCRNSSTCIPRRWLCDGDDCGDGSDETGCSAPASEPPGSL

CPANEFQCRNSSTCIPRRWLCDGDDCGDGSDETGCSAPASEPPGSL

CPANEFQCRNSSTCIPRRWLCDGDDCGDGSDETGCSAPASEPGSL

CPANEFQCRNSSTCIPRRWLCDGDDCGDGSDETGCSAPASEPPGSL

CPANEFQCRNSTCIPRRWLCDGDDCGDGSDETGCSAPASEPGSL

CPANEFQCRNSTCIPRRWLCDGDDCGDGSD
```

Please replace paragraph [384] beginning at page 107, line 32, with the following:

--[384] A library of DNA sequences encoding monomeric A domains was created by assembly PCR as described in Stemmer *et al.*, *Gene* 164:49-53 (1995). The oligonucleotides used in this PCR reaction are (SEQ ID NOS:435-465):

```
5'-ATTCTCACTCGGCCGACGGTGCCTACCCGT-3'
5'-ACGGTGCCTACCCGTATGATGTTCCGGATTATGCCCCGGGTCTGGAGGCGTCTGGTGGTTCGTGT-3'
5'-CGCCGTCGCAAMSCMASBBCNSTGRAABGCATNTKYYGKWAYYSYKGCATYYAAATTBGBYGRDAGVKTBACACGAACC
5 - - CGCCGTCGCAAMSCMASBBCNSTGRAABGCAKYKGCCGYTKYYGCATYYAAATTBGBYGRDAGVKTBACACGAACCACCAGA - 3 '
\verb§5'-CGCCGTCGCAAMSCMASBBCNSTGRAABGCATNTKYYGKWAYYSYKGCACBKGAACTSGYYCGVCNSACA
  CGAACCACCAGA-3'
5'-CGCCGTCGCAAMSCMASBBCNSTGRAABGCAKYKGCCGYTKYYGCACBKGAACTSGYYCGVCNSACACGAACCACCAGA-3'
5'-TTGCGACGGCGWWRATGATTGTSNGGACRRCTCGGATGAA-3'
5'-TTGCGACGGCGWWRATGATTGTSSGGACGGCTCGGATGAA-3'
5'-TTGCGACGGCGWWRATGATTGTSRGGACRRCTCGGATGAA-3'
5'-TTGCGACGGCGWWCCGGATTGTSNGGACRRCTCGGATGAA-3'
5'-TTGCGACGGCGWWCCGGATTGTSSGGACGGCTCGGATGAA-3'
5'-TTGCGACGGCGWWCCGGATTGTSRGGACRRCTCGGATGAA-3'
5'-AGGCCTGCAATGACGTABGCKBTKBACAGYYTKYTTCATCCGAGYYGTCC-3'
5'-AGGCCTGCAATGACGTABGTNCGGNSSYTBYACAGYYTKYTTCATCCGAGYYGTCC-3'
\verb§--AGGCCTGCAATGACACTTTGTGAAATTCCGGATCCTGGCTACAGYYTKYTTCATCCGAGYYGTCC-3 \\ \texttt{--3}
\verb§5'-AGGCCTGCAATGACAGGGAACCCGGCGGTTCAGATGCTGGCGCGCTACAGYYTKYTTCATCCGAGYYGTCC-3'
5'-AGGCCTGCAATGACGCTGCCGGTGCAGAAGTCGCACCTGGGCCCGGACGACCACAGYYTKYTTCATCCGAGYYGTCC-3'
5'-AGGCCTGCAATGACGTGCTCGGACCTGGGGTGCTAAACGGCAGAATATGAGAATCACCACAGYYTKYTTCATCCGAGYYGTCC-3'
5'-AGGCCTGCAATGACGTABGCKBTKBACAMWSCKSCGVTTCATCCGAGCCGTCC-3'
5'-AGGCCTGCAATGACGTABGTNCGGNSSYTBYACAMWSCKSCGVTTCATCCGAGCCGTCC-3'
5'-AGGCCTGCAATGACACTTTGTGAAATTCCGGATCCTGGCTACAMWSCKSCGVTTCATCCGAGCCGTCC-3'
5'-AGGCCTGCAATGACAGGGAACCCGGCGGTTCAGATGCTGGCGCGCTACAMWSCKSCGVTTCATCCGAGCCGTCC-3'
5 '- AGGCCTGCAATGACGCTGCCGGTGCAGAAGTCGCACCTGGGCCCGGACGACCACAMWSCKSCGVTTCATCCGAGCCGTCC-3 '
5'-AGGCCTGCAATGACGTGCTCGGACCTGGGGTGCTAAACGGCAGAATATGAGAATCACCACAMWSCKSCGVTTCATCCGAGC
5'-AGGCCTGCAATGACGTABGCKBTKBACAGDKWKCCRRCGVTTCATCCGAGYYGTCC-3'
5'-AGGCCTGCAATGACGTABGTNCGGNSSYTBYACAGDKWKCCRRCGVTTCATCCGAGYYGTCC-3'
\verb§5!-AGGCCTGCAATGACACTTTGTGAAATTCCGGATCCTGGCTACAGDKWKCCRRCGVTTCATCCGAGYYGTCC-3!
```

Appl. No. 10/693,057

Amdt. dated February 25, 2004

Reply to Notice to File Missing Parts of February 19, 2004

5'-AGGCCTGCAATGACAGGGAACCCGGCGGTTCAGATGCTGGCGCGCTACAGDKWKCCRRCGVTTCATCCGAGYYGTCC-3'

- $\verb|5'-AGGCCTGCAATGACGCTGCCGGTGCAGAAGTCGCACCTGGGCCCGGACGACCACGDKWKCCRRCGVTTCATCCGAGYYGTCC-3'| \\$
- 5'-AGGCCTGCAATGACGTGCTCGGACCTGGGGTGCTAAACGGCAGAATATGAGAATCACCACAGDKWKCCRRCGVTTCATCCGAGYYG TCC-3'
- 5'-TGAATTTTCTGTATGAGGTTTTGCTAAACAACTTTCAACAGTTTCGGCCCCAGAGGCCTGCAATGAC-3'

(R=A/G, Y=C/T, M=A/C, K=G/T, S=C/G, W=A/T, B=C/G/T, D=A/G/T, H=A/C/T, V=A/C/G, and N=A/C/G/T).

Please replace paragraph [387] beginning at page 108, line 29, with the following:

--[387] Phage from the final eluate was used directly, without purification, as a template to PCR amplify A domain encoding DNA sequences. The oligonucleotides used in this PCR reaction are:

- 5'-aagcctcagcgaccgaa (SEQ ID NO:466)
- 5'-agcccaataggaacccat (SEQ ID NO:467)--

Please replace paragraph [392] beginning at page 109, line 12, with the following:

--[392] Binding of the individual phage clones to their target proteins was analyzed by ELISA. Clones yielding the highest ELISA signals were sequenced and subsequently recloned into a protein expression vector. Exemplary sequences are provided below (SEQ ID NOS:468-475):

>CD28-A1

 ${\tt CGPGRFQCESGQCIPATWVCDGENDCVDDSDEKSCATTAPTCLPDQFQCHDYRRCIPLGWVCDGVPDCVDNSDEANCEPPT}$

>CD28-A2

CGPGRFQCESGQCIPATWVCDGENDCVDDSDEKSCATTAPTCPPDQFTCNSGRCVPLNWLCDGVNDCADSSDEPPEC QPRT

>CD28-A10

CGPGRFQCESGQCVPATWVCDGDDDCADGSDEKSCATTAPTCESNQFQCGSGQCLPGTWRCDGVNDCADSSDETGCG RPGPGATSAPAACGPGRFQCNNGNCVPQTLGCDGDNDCGDSSDEANCSAPASEPPGSL

>CD28-A4

 ${\tt CGPGRFQCESGQCIPATWVCDGENDCVDDSDEKSCATTAPTCPANQFQCGNGRCIPPAWLCDGVNDCGDGSDESQLC} \\ {\tt AATGPT}$

<u>PATENT</u>

Appl. No. 10/693,057 Amdt. dated February 25, 2004 Reply to Notice to File Missing Parts of February 19, 2004

>CD28-A5

 ${\tt CGPGRFQCESGQCIPATWVCDGENDCVDDSDEKSCATTAPTCLPNEFRCSNGQCIPPNWRCDGVDDCRDGSDEAGCS} \\ {\tt QDPEFHKV}$

>CD28-A7

 $\tt CGPGRFQCESGQCIPATWVCDGENDCVDDSDEKSCATTAPTCGSGQFRCSNGNCLPLRLGCDGVDDCGDSSDEPLDPCAATVRT$

>CD28-A17

 ${\tt CGPGRFQCESGQCIPATWVCDGENDCVDDSDEKSCATTAPTCPSGQFKCNSGRCVPPNWLCDGVNDCPDNSDEANCPPRT}$

>CD28-A19

 $\tt CGPGRFQCESGQCIPATWVCDGENDCVDDSDEKSCATTAPTCQADEFQCQSSGKCLPVNWVCDGDNDCGDDSDETNCATTGRT--$

Please replace paragraph [398] beginning at page 111, line 13, with the following:

--[398] A library of DNA sequences encoding monomeric A domains was created by assembly PCR as described in Stemmer *et al.*, *Gene* 164:49-53 (1995). The oligonucleotides used in this PCR reaction are (SEQ ID NOS:476-506):

- 5'-ATTCTCACTCGGCCGACGGTGCCTACCCGT-3'
- 5'-ACGGTGCCTACCCGTATGATGTTCCGGATTATGCCCCGGGTCTGGAGGCGTCTGGTGGTTCGTGT-3'
- 5'-CGCCGTCGCAAMSCMASBBCNSTGRAABGCATNTKYYGKWAYYSYKGCATYYAAATTBGBYGRDAGVKTBACACGAACC ACCAGA-3'
- 5'-CGCCGTCGCAAMSCMASBBCNSTGRAABGCAKYKGCCGYTKYYGCATYYAAATTBGBYGRDAGVKTBACACGAACCACCAGA-3
- 5'-CGCCGTCGCAAMSCMASBBCNSTGRAABGCATNTKYYGKWAYYSYKGCACBKGAACTSGYYCGVCNSACA CGAACCACCAGA-3'
- $\verb| 5'-CGCCGTCGCAAMSCMASBBCNSTGRAABGCAKYKGCCGYTKYYGCACBKGAACTSGYYCGVCNSACACGAACCACCAGA-3'| \\$
- 5'-TTGCGACGGCGWWRATGATTGTSNGGACRRCTCGGATGAA-3'
- 5'-TTGCGACGGCGWWRATGATTGTSSGGACGGCTCGGATGAA-3'
- 5'-TTGCGACGGCGWWRATGATTGTSRGGACRRCTCGGATGAA-3'
- ${\tt 5'-TTGCGACGGCGWWCCGGATTGTSNGGACRRCTCGGATGAA-3'}\\$
- 5'-TTGCGACGGCGWWCCGGATTGTSSGGACGGCTCGGATGAA-3'
- 5'-TTGCGACGGCGWWCCGGATTGTSRGGACRRCTCGGATGAA-3'
- 5'-AGGCCTGCAATGACGTABGCKBTKBACAGYYTKYTTCATCCGAGYYGTCC-3'
- 5'-AGGCCTGCAATGACGTABGTNCGGNSSYTBYACAGYYTKYTTCATCCGAGYYGTCC-3'
- 5'-AGGCCTGCAATGACACTTTGTGAAATTCCGGATCCTGGCTACAGYYTKYTTCATCCGAGYYGTCC-3'
 5'-AGGCCTGCAATGACAGGGAACCCGGCGGTTCAGATGCTGGCGCGCTACAGYYTKYTTCATCCGAGYYGTCC-3'
- 5'-AGGCCTGCAATGACAGGGAACCCGGCGGITCAGAIGCTGGCCCGGACCGACCACAGYYTKYTTCATCCGAGYYGTCC-3'
- 5'-AGGCCTGCAATGACGTGCTCGGACCTGGGGTGCTAAACGGCAGAATATGAGAATCACCACAGYYTKYTTCATCCGAGYYGTCC-3'
- 5'-AGGCCTGCAATGACGTABGCKBTKBACAMWSCKSCGVTTCATCCGAGCCGTCC-3'
- 5'-AGGCCTGCAATGACGTABGTNCGGNSSYTBYACAMWSCKSCGVTTCATCCGAGCCGTCC-3'
- $\verb§5'-AGGCCTGCAATGACACTTTGTGAAATTCCGGATCCTGGCTACAMWSCKSCGVTTCATCCGAGCCGTCC-3'$
- 5'-AGGCCTGCAATGACAGGGAACCCGGCGGTTCAGATGCTGGCGCGCTACAMWSCKSCGVTTCATCCGAGCCGTCC-3'
 5'-AGGCCTGCAATGACGCTGCCGGTGCAGAAGTCGCACCTGGGCCCGACGACCACAMWSCKSCGVTTCATCCGAGCCGTCC-3'
- 5 '-AGGCCTGCAATGACGTGCTCGGACCTGGGGTGCTAAACGGCAGAATATGAGAATCACCACAMWSCKSCGVTTCATCCGAGC
- 5'-AGGCCTGCAATGACGTABGCKBTKBACAGDKWKCCRRCGVTTCATCCGAGYYGTCC-3'
- 5'-AGGCCTGCAATGACGTABGTNCGGNSSYTBYACAGDKWKCCRRCGVTTCATCCGAGYYGTCC-3'
- 5'-AGGCCTGCAATGACACTTTGTGAAATTCCGGATCCTGGCTACAGDKWKCCRRCGVTTCATCCGAGYYGTCC-3'

Appl. No. 10/693,057

Amdt. dated February 25, 2004

Reply to Notice to File Missing Parts of February 19, 2004

5'-AGGCCTGCAATGACAGGGAACCCGGCGGTTCAGATGCTGGCGCGCTACAGDKWKCCRRCGVTTCATCCGAGYYGTCC-3'

- 5'-AGGCCTGCAATGACGCTGCCGGTGCAGAAGTCGCACCTGGGCCCGGACGACCACAGDKWKCCRRCGVTTCATCCGAGYYGTCC-3'
- 5'-AGGCCTGCAATGACGTGCTCGGACCTGGGGTGCTAAACGGCAGAATATGAGAATCACCACAGDKWKCCRRCGVTTCATCCGAGYYGTCC-3'
- $\verb§5'-TGAATTTTCTGTATGAGGTTTTGCTAAACAACTTTCAACAGTTTCGGCCCCAGAGGCCTGCAATGAC-3'$

 $(R=A/G,\ Y=C/T,\ M=A/C,\ K=G/T,\ S=C/G,\ W=A/T,\ B=C/G/T,\ D=A/G/T,\ H=A/C/T,\ V=A/C/G,\ and\ N=A/C/G/T) \ \underline{\quad \ } \ \underline$

Please replace paragraph [401] beginning at page 112, line 15, with the following:

--[401] Phage from the final eluate was used directly, without purification, as a template to PCR amplify A domain encoding DNA sequences. The oligonucleotides used in this PCR reaction are:

- 5'-aagcctcagcgaccgaa (SEQ ID NO:466)
- 5'-agcccaataggaacccat (SEQ ID NO:467)--

Please replace paragraph [404] beginning at page 112, line 25, with the following:

--[404] Clones were identified by the same methods as those described above for CD28. Identified clones included the following (SEQ ID NOS:507-511):

>116#4 >1L6#4

 ${\tt CLSSQFQCKNGQCIPQTWVCDGDNDCEDDSDETGCGDSHILPFSTPGPSTCPPSQFTCRSTNTCIPAPWRCDGDDDCEDDSDEEGCSAPASEPPGSL}$

>IL6#7

 ${\tt CLSSQFQCKNGQCIPQTWVCDGDNDCEDDSDETGCGDSHILPFSTPGPSTCRSNEFQCRSSGICIPRTWVCDGDDDCLDNSDEKDCAART}$

>IL6#9

 $\tt CRSDQFQCGSGHCIPQDWVCDGENDCEDGSDETDCSAPASEPPGSLCLSSQFQCKNGQCIPQTWVCDGDNDCEDDSDETGCGDSHILPFSTPGPST$

>IL6#P8

 ${\tt CRSDQFQCGSGHCIPQDWVCDGENDCEDGSDETDCSAPASEPPGSLCRSNEFQCRSSGICIPRTWVCDGDDDCLDNSDEKDCAART}.$

>IL6#N7

CPPSQFTCRSTNTCIPAPWRCDGDDDCEDDSDEADCGDSHILPFSTPGPSTCLSSQFQCKNGQCIPQTWVCDGDND CEDDSDETGCGDSHILPFSTPGPST--

PATENT

Please insert the accompanying paper copy of the Sequence Listing, page numbers 1 to 387, at the end of the application.